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Via e-mail to masten@niehs.nih.gov

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P.O. Box 12233, MD A3-07
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Re: 69 Fed. Reg. 52691—Announcement of and Request for Public Comment on Substances Nominated to the NTP for Toxicological Studies and Study Recommendations Made by the Interagency Committee for Chemical Evaluation and Coordination

Dear Dr. Masten:

On behalf of the members and supporters of People for the Ethical Treatment of Animals, the Animal Protection Institute, the Doris Day Animal League, and the Physicians Committee for Responsible Medicine, I wish to register our vehement opposition to the Interagency Committee for Chemical Evaluation and Coordination's (ICCEC) most recent recommendations for toxicological studies as outlined in the above-referenced *Federal Register* notice.

General Comments

As the parties to this submission and other public commenters have stressed repeatedly in previous submissions (i.e., PETA comments dated June 17, 2004 and July 8, 2004, attached, to which we have received neither a response nor an acknowledgement of receipt), the NTP's practice of actively soliciting nominations of chemicals that organizations and/or private individuals would like to see tested (almost invariably on animals) has led to a veritable laundry list of ill-conceived testing recommendations. Examples include proposals to conduct extensive animal testing of plant extracts that have been used without harm for generations as dietary supplements (e.g., grape seed and pine bark extracts), as well as proposals to retest such well-known hazardous substances as turpentine and antifreeze. Such recommendations defy not only common sense, but also fly in the face of the NTP's own stated "Vision for the 21st Century," which is "… to move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations" (NTP, 2004).

The NTP's current "visioning" exercise provides a rare opportunity for the Program and its federal agency members to modernize the toxicology paradigm under which they operate. The exorbitant costs associated with conventional forms of toxicity testing—both economic and in terms of animal suffering and death—could be dramatically reduced if regulatory agencies took greater advantage of *in vitro* and computational methods which are, or will soon be, validated and suitable for regulatory use, and moved away from the current approach of throwing every test in the book at substances of concern—which inevitably leads to "paralysis by analysis"—replacing it with timely and meaningful risk management measures. Movement along these lines would also bring the NTP's activities more into line with the following Congressional mandates, which have, thus far, been given inadequate consideration and fewer resources:

Mandate to Develop and Utilize Alternatives to Animal Testing

The National Institutes of Health (NIH) Revitalization Act, 42 *U.S.C.A.* §283e, directs the NIH, through an Interagency Coordinating Committee on the Use of Animals in Research, to prepare a plan to conduct or support research into methods of research that "do not require the use of animals," that "reduce the number of animals used in such research," that encourage the "acceptance by the scientific community" of alternative methods, and that trains "scientists in the use of such methods." 42 *U.S.C.* §283e.

Similarly, the central aim of the ICCVAM Authorization Act of 2000, 42 *U.S.C.* §2851 *et seq*, is "to establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness." In establishing ICCVAM as a permanent Committee, Congress signaled its firm commitment to the promotion and advancement of alternatives to animal-based toxicity testing.

Mandate to Ensure Test Method Validation and Data Quality

The ICCVAM Authorization Act also reflects Congress' intent that "each federal agency … shall ensure that any new or revised acute or chronic toxicity test method, including animal test methods and alternatives, is determined to be valid for its proposed use prior to requiring, recommending, or encouraging the application of such test method." 42 *U.S.C.* §2851-4(c). "Validation" is defined by ICCVAM and its international counterparts as "the process by which the reliability and relevance of a procedure are established for a particular purpose" (ICCVAM, 2003).

The Data Quality Act (DQA), 44 *U.S.C.* §3516 reflects Congress' further requirement that governmental agencies ensure the "quality, objectivity, utility, and integrity of information disseminated by the agency…." The DQA's Objectivity Standard, for example, requires federal agencies, and by extension the NTP itself, to ensure that information they disseminate is "accurate, reliable, and unbiased" (OMB, 2002; NIH, 2002). U.S. agencies have established a government-wide data quality standard that requires proper validation of toxicity test methods before data from such tests may be considered reliable:

> Before a new or revised test method is used to generate information to support regulatory decisions, it must be…validated to determine its reliability and relevance for its proposed use…. (ICCVAM, 2003).

Moreover, for Influential Scientific Information—such as data from NTP toxicity studies, which may ultimately be used by its member agencies as the basis for regulatory decisions—the NIH's own information quality guidelines (which are binding on all NIH sub-institutes, such as the National Institute of Environmental Health Sciences, which administers the NTP) assert that the "NIH is committed to applying rigorous scientific standards to ensure the accuracy, reliability, and reproducibility of research results" (NIH, 2002). However, the NIH/NIEHS/NTP cannot ensure the accuracy, reliability, and reproducibility of research results from toxicity studies until and unless these data are generated by reliable tests, and validation is necessary to ensure reliability (ICCVAM, 2003).

The NTP is further obligated to adhere to the DQA's Utility Standard, which requires that information disseminated by a federal agency be useful to its intended users, including the

public (OMB, 2002; NIH, 2002). Information from toxicity tests is not useful when it is generated from non-validated, and therefore potentially unreliable and irrelevant tests.

As expanded upon below, the ICCEC's current recommendations are an affront to the Congressional mandates outlined above: they do nothing to minimize animal testing, and indeed, call for extensive use of animals, including non-human primates; and they endorse the conduct of toxicity studies for which there are no standardized, much less validated, protocols, which is a violation of both the letter and the spirit of the Data Quality Act.

Specific Comments

The *Federal Register* notice cited above provides only the most superficial outline of the types of studies recommended by the ICCEC to be carried out with each compound. With the exception of di-(2-ethylhexyl)phthalate, tungsten trioxide and the perfluorinated compounds, the supporting documents for each compound (i) were apparently prepared by the ICCEC rather than by the nominating party, and (ii) are merely literature reviews, rather than details of the test plans/protocols. As we do not know which specific protocols or guideline studies are envisaged, it is not possible for us to prepare detailed critiques. However, our comments on the outline recommendations are as follows:

Bitter orange extract

The ICCEC has recommended that a wide range of toxicity studies be carried out on this natural substance, including developmental toxicity, cardiovascular toxicity, cerebrovascular toxicity, subchronic toxicity, and toxicokinetics. Further, the ICCEC has recommended that these studies be carried out on bitter orange extract both alone and in combination with caffeine, and that they be carried out in both rats and mini-pigs.

According to the literature review for this compound, the nomination of bitter orange extract is "based on its widespread and increasing use in 'ephedra-free' dietary supplements and limited data to demonstrate its safety for this use." The literature review further acknowledges that bitter orange is already regulated by the U.S. Food and Drug Administration (FDA), and that its peel, oil, extracts, and oleoresins are Generally Recognized as Safe as a direct additive to food. However, the ICCEC clearly paid little regard to this fact in formulating its testing recommendations.

The ICCEC's proposals also appear to be oblivious to the fact that bitter orange extract is not a single compound or a defined mixture of compounds. The ICCEC's testing proposals are not even clear as to which material the term "bitter orange extract" refers, because the *Federal Register* states that "bitter orange extract" does not have a CAS number, whereas the literature review states that the CAS number of "bitter orange peel extract" is 977081-87-0 (p. 2). This leaves open the possibility that these are two different materials, or perhaps that the latter is a sub-set of the former.

Bitter orange preparations are undefined mixtures of various compounds, including p-octopamine, p-synephrine, tyramine, N-methyltyramine, hordenine, and stachydrine. "Bitter oranges" also include at least two distinct varieties or sub-species: the European Seville orange, and the Chinese *zhi shi*. Therefore, data generated by toxicity studies on rats and mini-pigs will have no regulatory value whatsoever, because any results suggesting the extract to be toxic will be readily explicable as being due to inter-species difference, or differences between the chemical compositions of different batches of extract, or both. Clearly, toxicity studies on an

undefined mixture of compounds have the potential to expand almost exponentially. (Parenthetically, it should be noted that organochlorine residues are known to be extremely toxic, and they persist in citrus fruits and their products. This issue deserves far more urgent attention—both from a scientific and a regulatory perspective—than the hypothetical toxicity of naturally occurring compounds of the fruits.)

However, perhaps our most serious concern relates to the ICCEC's ongoing disregard for the DQA's requirement that information disseminated by federal agencies must be accurate, reliable, unbiased and useful. In the context of toxicology, these requirements are inextricably linked to the proper validation of the test methods used to generate the data. One of the pillars of validation is the determination of a test's reliability, which requires the generation of reproducible results both within and between labs using a standardized protocol and reference chemicals (ICCVAM, 2003). Whereas a number of the studies recommended by the ICCEC have at least been codified in internationally recognized testing guidelines (which by no means suggests that these tests have been properly validated), no such standardized protocols or test guidelines exist for cardiovascular and cerebrovascular toxicity. There can therefore be no question that (i) these studies have not been determined to be valid for their intended purpose, as required by the ICCVAM Authorization Act before their use is required, recommended or encouraged by a U.S. federal agency, and (ii) the use of resultant data for regulatory purposes by a U.S. federal agency would constitute a violation of the DQA. Accordingly, the parties to this submission call upon the ICCEC to rescind its testing recommendations for bitter orange extract.

As alternatives to the non-validated animal studies proposed by the ICCEC, we suggest the following:

1. *Epidemiology studies*. Bitter orange extracts are currently in wide use as dietary and supplements and medicines. However, the only information about the effects of the extract in humans are either anecdotal reports about individuals who consumed large quantities, or reports of small clinical studies on slimming tablets, which often contain bitter orange extracts together with stimulants (literature review, pp. 10-11). Therefore, what is essential at this stage is a full-scale epidemiology study.

2. *Analytical chemistry*. Only a relatively small number of samples of bitter orange extract have been analyzed chemically. One approach to assessment of the toxicity of this material would therefore be to carry out full chemical analyses of a large number of batches of bitter orange extract, obtained from all commercial manufacturers. Only when this has been done would a review of the toxicological literature, such as that provided in the supporting document, be valid. In addition, the toxicity of each component should be predicted by structure-relationship analysis, and the *in silico* techniques now available enable much more sophisticated analyses than those in the supporting document. Lastly, *in vitro* methods could be utilized to assess the toxicity of each component.

Finally, we note that the original nomination was submitted by an unnamed, "private individual." We consider it unacceptable for anyone to make a recommendation of this type yet remain unnamed. It is quite possible that this individual is employed by a relevant company, academic institution, or government agency, and therefore stands to gain financially or otherwise from the conduct of these studies. We see no reason why such an individual should be free to make recommendations of this type under cover of anonymity. This issue has been raised repeatedly by PETA (most recently in comments dated June 17, 2004 and July 8, 2004, attached), and we would very much appreciate the NTP's attention, and response, to this matter.

n-Butyl glycidyl ether (CAS no. 2426-08-6)

The ICCEC has recommended that various toxicity studies be carried out on this compound, includng reproductive toxicity, carcinogenicity, and metabolism. The ICCEC has recommended that these studies be coordinated "with voluntary data development activities of the US EPA" (*Federal Register*). However, the ICCEC fails to mention that a test plan for n-butyl glycidyl ether was submitted to the Agency by the Society of the Plastics Industry (SPI) in December 2001 under the EPA's High Production Volume (HPV) Challenge Program, and that a revised plan was submitted in September 2002 (see http://www.epa.gov/chemrtk/nbtglyet/c13352tc.htm). In the company's own words: "Based upon the extensive examination of reproductive organs in these studies, no further testing for reproductive effects is considered necessary. This conclusion is also supported by guidance presented in EPA's guidance document for meeting HPV requirements wherein it is recommended that if you have an adequate 90-day study that looks at reproductive organs, then a separate reproductive toxicity study is not necessary." In view of this conclusion, there would appear to be no justification for the ICCEC's call for a reproductive toxicity study.

With respect to tests on toxicity other than reproductive toxicity, we must stress that an enormous amount of research on the toxicity of n-butyl glycidyl ether has been carried out, including metabolism studies that are not included in the references in the supporting document (Eadsforth, 1985). See also http://www.epa.gov/chemrtk/nbtglyet/c13352pm.htm. In the test plans for the EPA's HPV Program, the SPI stated its intention to carry out a developmental study, in response to which the Physicians Committee for Responsible Medicine (PCRM) pointed out that at least two developmental toxicity studies had previously been carried out (see http://www.epa.gov/chemrtk/nbtglyet/c13352pm.htm). However, in spite of PCRM's comments, SPI has presumably now carried out the proposed developmental study, in which case yet more data will be available. The need for more animal data should be justified far more carefully than is done in the ICCEC's recommendation before any additional animal studies are proposed.

Finally, one area where there is a definite shortage of data is industrial exposure and toxicity; no data are available on human chronic exposure and toxicity (literature review, p. 8). We therefore urge the ICCEC to rescind its testing recommendations for n-Butyl glycidyl ether and recommend that one or more human epidemiology studies be undertaken instead.

Di-(2-ethylhexyl)phthalate (DEHP; CAS no. 117-81-7)

It should be noted that the CAS number provided by the ICCEC in the *Federal Register* (118-71-7) is incorrect (which, frankly, does not inspire confidence in the care taken by the ICCEC in making its recommendations).

In its nomination of DEHP (p. 10), the FDA proposes the following animal-based studies:

(i) Metabolism studies in neonatal male and pregnant female monkeys

(ii) A metabolism and immunotoxicity study in neonatal rats

(iii) Dependent upon the results of (i), metabolism and immunotoxicity studies in neonatal male monkeys

As with the substances previously discussed, an enormous number of toxicity studies have already been carried out on DEHP. Some of these studies are referenced in the nomination; however, it should be noted that the literature review provided by the ICCEC is far from comprehensive, as a number of relevant studies—including several on neonatal toxicity—were apparently overlooked or otherwise excluded from the literature review (e.g., Gollamudi, 1985; Parmar, 1985; Agarwal, 1986; Dostal, 1987, 1988; Sjoberg, 1988; Li, 2003; Masuo, 2004). In addition to the enormous amounts of published data, there are also plans to include DEHP as part of the Organization for Economic Cooperation and Development (OECD) SIDS Program (see http://www.tsgusa.com/hpv97.pdf). DEHP is also included within the phthalate esters category in the EPA's HPV Program (see http://www.epa.gov/chemrtk/benzene/c13467tp.pdf).

Here again, the FDA and ICCEC are also recommending toxicity studies that have not been subject to formal or adequate validation. Indeed, although test guidelines do exist for both metabolism and immunotoxicity (i.e., OECD 417, OPPTS 870.7485 and 870.7800), the assessment of effects in neonates was clearly not envisaged when these guidelines were developed. For example, the EPA immunotoxicity test guideline (i.e., OPPTS 870.7800) specifies that: "Dosing should begin when the test animals are between six and eight weeks old." It is therefore clear that (i) these studies have not been determined to be valid for their intended purpose, as required by the ICCVAM Authorization Act before their use is required, recommended or encouraged by a U.S. federal agency, and (ii) the use of resultant data for regulatory purposes by a U.S. federal agency would constitute a violation of the DQA. As such, we call upon the ICCEC to rescind its testing recommendations for DEHP, in favor of an epidemiological approach in humans—particularly in view of the FDA's assertion that "data in humans are lacking" (FDA nomination, p. 4).

Ionic liquids (CAS nos. 79917-90-1, 479500-35-1, and 1124-64-7)

Consistent with the chemical nomination by the U.S. EPA, the ICCEC has recommended the full toxicological characterization of three ionic liquids. We agree that little information is available about the toxicity of these compounds; however, it is highly premature to propose animal-based toxicity studies, given that only one *in vitro toxicity* study has been carried out, on 1-butyl-3-methylimidazolium chloride (CAS no. 79917-90-1; literature review, p. 16). We therefore urge the ICCEC to rescind its animal testing recommendations in favor of a battery of *in vitro* mechanistic studies and *in silico* structure-activity analyses (as opposed to the simple database search proposed in the EPA's nomination).

Perfluorinated compounds (CAS nos. 375-73-5, 355-46-4, 1763-23-1, 474511-07-4, 335-77-3, 79780-39-5, 307-24-4, 335-67-1, 375-95-1, 335-76-2, 307-55-1, 678-39-7, and 865-86-1)

The EPA's nomination of perfluorinated compounds recommends a total of 31 animal-based studies, consisting of 10 range-finding studies, 10 pharmacokinetics studies, 10 one-generation reproductive toxicity studies, and a two-year chronic and developmental toxicity study. However, a detailed literature review has not been provided. In fact, the only supporting documentation included is a 9-page letter/nomination from the EPA. The ICCEC's uncritical endorsement of this chemical nomination is completely unsatisfactory, as little justification for the studies is given, and no references are provided. We therefore call upon the ICCEC to rescind its testing recommendations for these perfluorinated compounds and recommend the following alternative approach in their place:

1. *Compound categorization*. The nomination states that extensive toxicology and pharmacokinetics information is available for three of the compounds. Some attempt should therefore be made to apply these data to the other compounds. In particular, the 13 compounds form three clear categories: (i) pefluoroalkane sulfonic acids (CAS nos. 375-73-5, 355-46-4, 1763-23-1, 474511-07-4, 335-77-3, 79780-39-5), (ii) perfluorocarboxylic acids (CAS nos. 307-24-4, 335-67-1, 375-95-1, 335-76-2, 307-55-1), and (iii) telomer alcohols (CAS nos. 678-39-7, 865-86-1). Within each of these categories, the difference between compounds is solely one of alkyl straight-chain length, and the difference in toxicity and pharmacokinetics should therefore be fairly predictable. The two compounds about which the most toxicology information is available are one compound in the pefluoroalkane sulfonic acid category (perfluorooctanesulfonic acid, CAS no. 1763-23-1) and one in the perfluorocarboxylic acid category (perfluorooctanoic acid, CAS no. 335-67-1). It is therefore almost certain that the number of animal studies could at least be greatly reduced by categorization of compounds.

2. *Epidemiology studies*. Large numbers of workers are industrially exposed to these compounds. This therefore presents an ideal opportunity for epidemiology studies. We also call the NTP's attention to a recently announced collaborative study between the EPA, the Centers for Disease Control and Prevention, and the American Chemistry Council. The study will track household exposures and effects of several priority substances, including perfluorinated compounds, on 60 children aged three-years and younger (28 Chem. Reg. Reporter 1066, 10/18/04).

The foregoing notwithstanding, the parties to this submission question whether any more data are actually needed. It is known that at least some of these compounds are toxic to animals. It is also known that they biopersistent and non-biodegradable, and that some of them bioaccumulate in fish. It therefore seems to go almost without saying that their presence in the environment is harmful, and the central task now should not be to generate further data, but to find alternatives to their use, to decrease human exposure, spillage, and disposal in industrial use, and to make the regulations governing their use stricter and more enforceable. As with a number of other test proposals, this nomination appears to be a thinly veiled smokescreen to justify further delays and regulatory inaction by the EPA.

<u>*Stachybotrys chartarum* (CAS no. 67892-26-2)</u>

The ICCEC has recommended that studies be carried out on the general toxicity and immunotoxicity of this fungus.

There has been a great deal of concern over the last few years about *S. chartarum*, popularly known as "toxic mold," which is thought to be partly responsible for sick-building syndrome. However, it must first be recognized that *S. chartarum* is not a species in any strict sense, but rather a catch-all term for ascomycetes that look similar in terms gross morphology, and are only known to reproduce asexually; thus, because fungal taxonomy is mostly based on the characteristics of the sexual stage, they cannot be classified more precisely (literature review, p. i). *S. chartarum* produces an extraordinarily wide range of mycotoxins, including satratoxins, roridins, verrucarins, and stachybocins (literature review, p. 3), in addition, some compounds not reported to be toxic may still be immunotoxic, such as stachylysin, spirolactones, spirolactams, cyclosporins, atranones, trichodieme, and diterpenes (p. 4). However, these compounds vary widely between the *S. chartarum* samples collected from different sites (it is not really accurate to describe these as strains). Thus, less than two-thirds of the *S. chartarum* samples that have been collected produce any mycotoxins at all (p. 6), and the mycotoxins that are produced

differ widely. The obvious approach to the taxonomy of *S. chartarum* is by genomic analysis. A start has been made in this area, and polymerase chain reactions have been carried out with four different sets of primers (p. 11). However, it is unclear whether these primers will detect all *S. chartarum* samples, or whether they reliably distinguish *S. chartarum* from other types of mold. In other words, the taxonomic status of *S. chartarum* is still highly uncertain. Furthermore, there is no information at all about whether the different sets of mycotoxins, etc., produced by *S. chartarum* correspond to different sub-taxa. As is stated in the literature review: "Except for identification of species-specific sequences for detection in environmental samples, little molecular work has been done" (p. 12).

Toxicity data for *S. chartarum* currently have even less value than those of bitter orange extract. The data refer to an indefinitely large group of species, which may or may not be closely related, and which produce an enormously large and wildly varying number of chemical compounds, of which some are recognized as toxins and others are not. It is difficult to see how exact science can be done under these circumstances, or how animal data could possibly hope to be relevant to humans (even leaving aside the problem of animal/human inter-species variation). An enormous number of toxicology reports relating to *S. chartarum* have been published. However, the ICCEC merely states that "toxicological characterization" is needed, without detailing the "gaps" in the toxicological database that are perceived to exist (i.e., based on the qualifier on the NTP's website, http://ntp-server.niehs.nih.gov/ntpweb/index.cfm?objectid= FD36284D-A72E-9607-28E1A439613A94ED, are we to assume that the ICCEC is proposing studies for genotoxicity, subchronic toxicity and chronic toxicity/carcinogenicity?). If this is the case, we strongly object, and urge the ICCEC to repeal its testing recommendations for *S. chartarum*, in favor of the following strategy:

1. *Chemical analysis*. Once the *S. chartarum* sub-taxa (which may be unrelated species or genera) have been distinguished, the sets of mycotoxins produced by each must be identified.

2. *In silico and in vitro toxicology*. Once the various sets of chemicals have been identified, their toxicities can be predicted by structural analysis and *in vitro* test methods.

3. *Epidemiology*. Enormous numbers of people are routinely exposed to *S. chartarum* (supporting document, p. 18). Many farmers and factory-workers are occupationally exposed to moldy grain, plant-based textiles, hay, straw, and paper, and enormous numbers of people are exposed through household or workplace mold, with one finding being that 6% of all buildings are contaminated. Especially in poorer countries, people are also exposed through eating moldy grains or pulses (El-Kady, 1991). We therefore consider that *S. chartarum* offers an almost ideal subject for large-scale human epidemiology studies. However, no such study has been carried out.

<u>Tungsten trioxide (CAS no. 1314-35-8)</u>

The ICCEC has recommended that numerous studies on the toxicity of this compound be conducted, covering general toxicity, genotoxicity, fiber stability, fiber biopersistence, pulmonary toxicity, intratracheal toxicity studies comparatively with a fiber known to be hazardous, and carcinogenicity. However, the nomination provides no further information about the proposed studies, and we therefore cannot critique the proposal in detail other than to point out, yet again, that a number of the recommended studies have not only not been validated, but have not even been standardized or codified as recognized test guidelines.

Additionally, it is unclearexactly which materials are included within the nomination. The CAS number applies to tungsten trioxide only, and much of the nomination seems to apply to this compound. However, at some points the recommendation seems also to cover tungsten metal (e.g., the nomination-rationale column in the *Federal Register* and p. 2 of the nomination), and at other points it seems to cover several tungsten suboxides (nomination, pp. 1, 4), and/or tungsten carbide (p. 2). This lack of clarity is unacceptable.

Tungsten was one of the materials in the ICCEC's 2003 recommendations, and, if it is included in the nomination, reference should be made to PETA's previous comments on those recommendations. Even if tungsten is not included, tungsten trioxide is closely associated with the refining and use of tungsten, and it is difficult to understand why no reference has been made to the 2003 nomination.

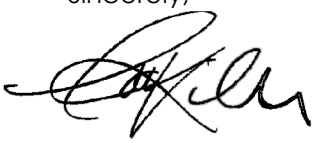
Even if the recommendations are assumed to be restricted to tungsten trioxide, a number of animal-based toxicity studies have already been carried out (nomination, pp. 11-12), including some that are not mentioned in the nomination (e.g., Roser, 1972). Furthermore, tungsten trioxide has been shown, repeatedly and over four decades, to be a serious industrial toxicant (Mogilevskaya, 1961; Brakhnova, 1975; Sahle, 1994, 1996). It therefore seems clear that the best way to safeguard the health of workers is to tighten the regulations relating to exposure, and to enforce current regulations effectively.

Furthermore, in the industrial environment, tungsten trioxide dust almost invariably occurs in association with the dust of silicon dioxide, tungsten metal, other tungsten compounds, and other rare earth compounds. Many of these are known to be toxic and/or carcinogenic, and the carcinogenicity of tungsten trioxide alone is therefore largely irrelevant. Once again, the most important issue with respect to tungsten trioxide toxicity is the making of technical, regulatory, and enforcement-wise progress in reduction of industrial exposure. We suspect that further toxicity studies are likely to act primarily as a smokescreen. We therefore call upon the ICCEC to rescind these testing recommendations for tungsten trioxide.

Conclusion

Even a cursory review of the ICCEC's testing recommendations reinforces our contention that the NTP's active solicitation of chemical nominations promotes sloppy toxicology that represents an appalling waste of taxpayer dollars and total disregard of Congressional mandates to ensure test method validation and data quality and to develop and utilize alternatives to animal testing. The NTP's chronic non-responsiveness to our concerns and repeated correspondence on this issue is unacceptable. On behalf of the more than one million Americans represented by the parties to this submission, we hereby request the NTP's immediate attention, and prompt response, to this critical matter. We further call upon the NTP to take no action based on ICCEC recommendations and to discontinue future solicitations of chemical nominations pending the finalization of the NTP Vision and Roadmap for the 21st Century.

Sincerely,



Troy Seidle
Director of Science Policy

Literature Cited

Agarwal DK et al. Effects of di(2-ethylhexyl) phthalate on the gonadal pathophysiology, sperm morphology, and reproductive performance of male rats. Environmental Health Perspectives 65, 343-350 (1986).

Brakhnova IT. Toxic effect of refractory compounds and measures for preventing occupational diseases among workers in powder metallurgy plants. Studies in Soviet Science: Environmental Hazards of Metals Toxicity of Powdered Metals and Metal Compounds, pp. 115-159, 231-249. New York: Consultants Bureau (1975).

Chemical Regulation Reporter. EPA, Chemistry Group Join in Project to Study Children's Household Exposure. 28 Chem. Reg. Reporter 1066, 18 Oct 2004.

Dostal LA et al. Hepatic peroxisome proliferation and hypolipidemic effects of di(2-ethylhexyl)phthalate in neonatal and adult rats. Toxicology and Applied Pharmacology 87, 81-90 (1987).

Dostal LA et al. Testicular toxicity and reduced Sertoli cell numbers in neonatal rats by di(2-ethylhexyl)phthalate and the recovery of fertility as adults. Toxicology and Applied Pharmacology 95, 104-121 (1988).

Eadsforth CV et al. n-Butylglycidyl ether: The formation of a novel metabolite of an epoxide. Drug Metabolism and Disposition 13, 263-264 (1985).

El-Kady IA et al. Mycotoxin production on different cultivars and lines of broad bean (*Vicia faba L.*) seeds in Egypt. Mycopathologia 113, 165-169 (1991).

Gollamudi R et al. Developmental changes in the conversion rates of di(2-ethylhexyl) phthalate to monoethylhexyl phthalate in rats. Journal of Toxicology and Environmental Health 15, 459-465 (1985).

ICCVAM [Interagency Coordinating Committee on the Validation of Alternative Methods]. ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods – NIH Publication No: 03-4508. Research Triangle Park, NC, USA: ICCVAM/NICEATM. (2003).

Li H et al. Effects of mono-(2-ethylhexyl) phthalate on fetal and neonatal rat testis organ cultures. Biology of Reproduction 69, 1964-1972 (2003).

Masuo Y et al. Effects of neonatal treatment with 6-hydroxydopamine and endocrine disruptors on motor activity and gene expression in rats. Neural Plasticity 11, 59-76 (2004).

Mogilevskaya OY. Effect on the body of artificial dust mixtures (rare earth metal oxides mixed with silicon dioxide. Gigiena i Sanitariia 26, 18-23 (1961).

Myhre BA. Toxicological quandary of the use of bis (2-diethylhexyl) phthalate (DEHP) as a plasticizer for blood bags. Annals of Clinical Laboratory Science 18, 131-140 (1988).

NIH [National Institutes of Health]. Guidelines for Ensuring the Quality of Information Disseminated to the Public, 21 pp. Website http://www.hhs.gov/infoquality/nih.html. (2002).

NTP [National Toxicology Program]. Toxicology in the 21st Century: The Role of the National Toxicology Program, 4 pp. Website http://ntp.niehs.nih.gov/ntp/main_pages/NTPVision.pdf. Research Triangle Park, NC (2004).

OMB [White House Office of Management and Budget]. Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies. 67 FR 8452. Website: http://www.whitehouse.gov/omb/fedreg/reproducible2.pdf. Washington, DC: OMB (2002).

Parmar D et al. Hepatic mixed function oxidases and cytochrome P-450 contents in rat pups exposed to di-(2-ethylhexyl)phthalate through mother's milk. Drug Metabolism and Disposition 13, 368-370 (1985).

Roser B et al. Prolonged lymphocytopenia in the rat: The immunological consequences of lymphocyte depletion following injection of 185W tungsten trioxide into the spleen or lymph nodes. Australian Journal of Experimental Biology and Medical Science 50, 185-198 (1972).

Sahle W et al. Airborne tungsten oxide whiskers in a hard-metal industry: Preliminary findings. Annals of Occupational Hygiene 38, 37-44 (1994).

Sahle W et al. Preliminary data on hard metal workers exposure to tungsten oxide fibres. Science of the Total Environment 191, 153-167 (1996).

Sjoberg P et al. Metabolism of mono-(2-ethylhexyl)phthalate in fetal, neonatal and adult rat liver. Biology of the Neonate 53, 32-38 (1988).